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A clinical study to evaluate the efficacy and safety of *Bacopa* caplets in memory and learning ability: a double blind placebo controlled study

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Bacopa has been used in the Ayurvedic system of medicine as a nervine tonic for centuries. The present study was carried out to evaluate the safety and efficacy of *Bacopa* caplets to improve memory and learning ability in a double blind placebo controlled clinical study. *Bacopa* caplets were given in a dose of one caplet (750 mg) daily for sixteen weeks. Verbal span test, verbal working memory task test and text comprehension tests were used as clinical parameters to assess memory and learning ability in 84 subjects. *Bacopa* caplets significantly improved these parameters at sixteen weeks of drug therapy. The drug was well tolerated without any serious adverse effects. It did not change any biochemical parameters. *Bacopa* caplets appear to be clinically effective in improving cognitive functions without any serious adverse effects.

Key words: *Bacopa*, cognitive function, efficacy, safety.

Introduction

Memory is an integral part of our existence, yet it is only vaguely understood. It is the ability to retain and utilise acquired information or knowledge.

Throughout the modern history of neuroscience, memory and attention have enjoyed centre stage as a fundamental process of intellectual function. Both operate together, memory has a limited capacity and hence attention determines what will be encoded. Attention operates in a world that is relatively stable over time and hence both memory and attention might reflect the same process. Attention helps to improve memory and encoding, but the details of this modulation remain unsolved (Chun 2007, Roediger 1990).

One of the most important conceptual developments in cognitive therapy is the subdivision of memory into three separate processes, encoding, storage and retrieval. Storage is difficult to study where the retrieval process is easiest to observe. A major question in many people's minds is how to improve memory. Medications such as modafanil, donepezil and racemic amphetamine have been used to improve memory in humans. But most of them have serious adverse effects.

Recently interest in the use of herbal products has grown dramatically both in developing countries and the Western world (Sparreboom 2004). It is now apparent those available psychotherapeutic agents are not sufficient to meet the therapeutic requirements of patients with mental illness. In the folklore of Indian medicine, several herbs have been traditionally used as nerve tonics. One of the most popular of these herbs is *Bacopa monnieri* (BM), a well known memory booster (Husain 2007). BM, also referred to as water hyssop, brahmi or jalanimba in India, has been used for centuries in the Ayurvedic system of medicine, a holistic system of medicine originally from India. The name brahmi is derived from the word 'brahma' the mythical 'creator' in the Hindu pantheon. It is classified as a medha rasayana, a drug used to improve memory and intellect (medhya) (Mukheijee 1966). The plant has been used extensively as a nootropic and digestive and to improve learning and memory (Nadkarni 1988).

Compounds responsible for the pharmacological effect of BM include alkaloids, saponins and sterols (Bose 1931). Alkaloids such as brahmine, nicotine and herpestine have been also reported to help in its pharmacology (Chopra 1956). A major chemical entity shown to be responsible for neuropharmocological effects is bacoside (Chatterji 1965). Bacoside is a complex of bacoside A and bacoside B, probably optical isomers. It is suggested that bacoside induces membrane dephosphorylation, with a concomitant increase in protein and RNA turnover in specific brain areas (Singh 1988) and helps in motor learning (Aithal 1961). Bacoside rich extracts of BM have been evaluated for reversing depletion of acetylcholine in the frontal cortex and hippocampus (Sairam 2001).

Recently *Bacopa* caplets have been introduced into clinical practice. They contain extracts of *Bacopa monnieri* 100 mg and powders of *Bacopa monnieri* 650 mg to be taken in a dose of 1 caplet daily. The present study evaluated the clinical efficacy and safety of *Bacopa*

caplets in individuals with disturbances in concentration, memory and learning ability.

Subjects

Ninety six subjects who were not taking any medication or other herbal preparation and who reported no head injury, entered into the study. Before entry each subject was given a detailed description of the investigational product, nature and duration of the study. Twelve participants, seven from the placebo group and five from the drug treated group withdrew from the study after the initial testing session for personal reasons. None of them withdrew because of any adverse effect due to medication. Eighty four participants (52 females and 32 males) between the age of 30 and 42 (mean 36, SD 4) completed the study.

Design

The study was designed as a double blind randomised placebo control with two groups, a *Bacopa monnieri* group (n=41) and a placebo group (n=43).

Methods

The trial had a 3 week placebo run in with 12 weeks of treatment with either *Bacopa* or placebo. Participants were taken into the study as volunteers, living with family, taking no medication, with no complaint of memory problems and without any illness. They were educated with adequate Bengal language skills and adequately corrected vision. They were asked to refrain from alcohol for 24 hours prior to each visit and not to change life style habits during the study period. They provided informed consent and the study was approved by the local ethics committee. They were free to withdraw from the study if they so desired.

Intervention

The intervention was in the form of 12 weeks of a daily tablet comprising extract of *Bacopa monnieri* whole plant 100 mg and powders of *Bacopa monnieri* whole plant 650 mg. This extract was manufactured from the dried aerial plant of BM in India. The herb was extracted with water to produce 15% dry extract with a minimum of 60% of total bacoside, the plant was identified by a well qualified botanist and a voucher copy of the plant is preserved in pharmacognosy laboratory. Placebo was manufactured using excipient and replicated the active in appearance, odour and texture. Randomisation was determined by a computer generated series. All study personnel were blinded to the assignment until analysis.

Composition

Each caplet contains:

- Extract *Bacopa monnieri* whole plant 100 mg
- Powder *Bacopa minnieri* whole plant 650 mg

Good agricultural and collection practice (GACP) was followed during the collection and manufacture of the herbal formulation (WHO 2003). Botanical identification and Ayurvedic criteria for desired quality were in accordance with the guidelines of *Pharmacopoeial Standards of Ayurvedic Formulations* (1987) and were carried out by a qualified chemist approved by the Food and Drug Administration.

Bacopa monnieri, a semi aquatic herb, grows throughout India and is transplanted during September to November. Geographical source and harvest time for the herb was recorded. This formulation has been approved by regulatory authorities in India as a herbal formulation.

Assessment

Assessment was carried out initially and at monthly intervals until the end of the study. The assessment included a verbal memory battery designed for this study. All tasks proposed a reading input activity.

1. Verbal span test (Maria 2005) used to assess the general capacity of encoding verbal information. Participants read three different series of frequent words, which they were asked to recall randomly.The examiner recorded the number of words correctly recalled. The series was composed of phonologically similar words [bangle (bala), garland (mala), brother-in-law (sala)]. It also included long words such as current or running (cholito bhasha), name (pundarikaksha), guest (aaguntak), sweet (jolbhara sondesh), poem (shesher kovita).
2. Verbal working memory task (Daneman 1980) consists of reading several long sentences while retaining in memory the last word of each sentence. Participants were presented with three series of sentences and asked to recall the last word of each sentence.
3. Text comprehension test (logical memory) (Kintsch 1978). A story was presented to the participants and the subject was asked to recall the information in the text with details after reading it once.

For each compiled task the subject received 1 point or a 0 score; in the repetitive tasks the maximum score was 2; the event based task was 4.

Safety test

The subjects underwent hematological evaluation on entry and at the end of the study. All adverse events either reported or observed by patients were recorded with information about severity, duration and action taken regarding the study drug. The relationship of adverse events to the study medication was predefined as ‘unrelated’ (a reaction that does not follow a reasonable temporal sequence from the time of administration of the drug), ‘possible’ (follows a known response pattern to the suspected drug but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient), and ‘probable’ (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state). For patients recorded

as withdrawing from the study, efforts were made to ascertain the reason for the dropout. Non compliance (defined as failure to take less than 80% of the medication) was not regarded as treatment failure and reasons for non compliance were recorded.

Primary and secondary outcome measures

The predefined primary outcome measure was the effect of BM on memory and learning ability. The predefined secondary outcome was incidence of adverse effects and patient compliance.

Statistical analysis

Statistical analysis was carried out using Fisher's Exact test for presence or absence of various signs. Repeated measures of ANOVA followed by Dunnett's Multiple comparison and Posthoc were used for analysis of hematological parameters. Changes in memory and learning ability were analysed using paired 't' test. Values were expressed mean ± SD. The minimal level of significance was fixed at $p<0.05$. Statistical analysis was carried out using GraphPad Prism version 4.03.

Results

There were 96 subjects who were available for recruitment, 12 withdrew for personal reasons. The majority of the subjects were women of Asian origin. Average age was 36.0±4 and educational level was high school (Table 1). No difference existed between the groups for age, blood pressure, heart rate, temperature or education level. Mean score for tests of memory and learning are shown in Table 2. *Bacopa* drug therapy significantly improved verbal span memory, verbal working memory and logical memory at 16 weeks of drug therapy; placebo group did not show any such change. Placebo run in period did not indicate any significant changes in any of the parameters. Similarly no significant effects were observed on blood pressure, hematology, liver function tests, renal function test and fasting blood sugar.

Table 1: Demographic data

		Bacopa (n=41)	Placebo (n=43)
Age (mean ± SD) years		36.0 ± 4	35±2
Sex M/F		15/26	17/26
Education status	High school level	41	43
Mean blood pressure	Systolic and diastolic	120/80	110/80

Discussion

The present study indicates that *Bacopa* caplets when given for sixteen weeks are well tolerated in adults and help in improvement in cognitive function. *Bacopa* improved verbal span tests, verbal working memory task and text comprehension task where placebo recipients remained stable on these tasks. The benefits of *Bacopa* in cognitive functions have been reported in a number of other studies (Stough 2001, Roodenrys 2002).

The exact mechanism of action of *Bacopa* in enhancing mental activity is unknown, however the

Table 2: Mean score for memory and learning testslts

	Bacopa (n = 41)			Placebo (n = 43)		
Task	On entry	4 week	16 week	On entry	4 week	16 week
Verbal span: Short words Long words	 5.2±1.2 4.8±0.9	 5.4±0.8 5.1±0.8	 6.9±0.6* 6.8±0.5*	 5.3±1.6 4.9±0.9	 5.4±1.5 5.1±1.0	 5.6±1.2 5.2±1.8
Verbal working memory	9.2±1.8	9.6±1.2	12.37±1.4*	9.4±1.2	10.1±2.3	9.5±1.4
Logical memory	10.1±1.9	12.1±2.4	14.5±1.8*	10.8±2.0	10.9±2.1	11.1±1.9

Table 3: Effect of drug therapy on hematological parameters

Parameters		Before treatment	After treatment	Before treatment	After treatment
		Bacopa monnieri		Placebo	
Haemoglobin (gm/dl)		13.23±1.15	13.55±2.14	13.00±1.31	14.50±1.52
E.S.R. (mm/hr)		6.16±1.74	5.10±1.55	8.33±2.05	7.55±1.05
Total WBC count (cells/cu.mm3)		6453.00	6250.00	6671.00	6570.50
SGPT	IU/L	17.42	16.45	**18.21**	**17.50**
SGOT	IU/L	22.22	23.50	**24.55**	**24.35**
Serum creatinine	mg/dL	0.96	0.98	**0.94**	**0.96**
Total bilirubin	mg/dL	1.0	0.5	**0.8**	**0.5**
Mean FBS (mg %)		94.40	90.50		
		SD 8.53	9.57		

triterpenide saponins and their bacosides are responsible for the ability of *Bacopa* to enhance nerve impulse transmission. The bacosides aid in repair of damaged neurons by enhancing kinase activity, neuronal synthesis and restoration of synaptic activity (Singh 1997). Studies have also indicated that *Bacopa* extract modulates the expression of certain enzymes involved in generation and scavenging of reactive oxygen species in the brain (Chowdhuri 2002). Therapeutic doses of *Bacopa* are not associated with any known side effects and *Bacopa* has been used safely in Ayurvedic medicines for several hundred years.

Further studies may be required to determine whether the advantageous effects of *Bacopa* are due to its direct effect on brain chemistry to influence memory processes. A larger sample size will be useful for pharmacovigilance.

Conclusion

The present study indicates that *Bacopa* caplets are safe and efficacious in improving cognitive functions in human subjects. *Bacopa* drug therapy significantly improved verbal span memory, verbal working memory and logical memory at 16 weeks of drug therapy. The formulation is safe without any serious adverse effects. The drug is well tolerated.

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Disclosure of conflicting interest

Dr Pralhad S Patki and Dr Suprabha Hegde are full time employees of The Himalaya Drug Company. Dr Asim Kumar Mandal is a clinical tutor at Kolkata and has no financial interest in The Himalaya Drug Company.